Extradiol Oxygenation of 3,5-Di-*tert*-butylcatechol with O_2 by Iron Chlorides in Tetrahydrofuran–Water as a Model Reaction for Catechol-2,3-dioxygenases

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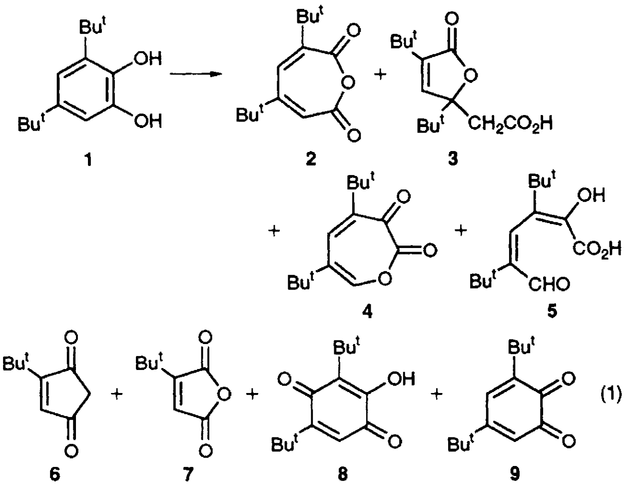
Selective extradiol oxygenation of 3,5-di-*tert*-butylcatechol **1** with O_2 catalysed by Fe^{2+} is achieved in THF in the presence of water; the different selectivity obtained by $FeCl_2$ and $FeCl_3$ in THF–H_2O and THF–pyridine supports the explanation of the intra- and extra-diol oxygenations by Fe^{3+} and Fe^{2+}, respectively, as proposed in the enzymatic systems.

Catecholdioxygenases are the central objects in the studies of dioxygenases since discovery of insertion of molecular oxygen into pyrocatechol to form muconic acid. Great efforts have been made for clarifying the mechanism from enzymatic and model chemistry aspects, but many problems are left unclear in the reaction steps in the cleavage of the carbon–carbon bonds with insertion of oxygen and in the mechanism of the selectivity control. Since the discovery of the intradiol oxygenation of **1** with cleavage observed between C(1) and C(2) by a bipyridine(pyridine)iron complex in THF,[2] the mechanism of the intradiol oxygenation by iron(III) oxygenases such as pyrocatechase has been discussed on the basis of results obtained for iron(III) complexes as function models.[3] However, extradiol oxygenation, with cleavage between the C(1) and C(6) or C(2) and C(3) carbons atoms, has received little study in terms of model systems. This is because Fe^{2+} is liable to be oxidized to Fe^{3+} and catechol is little activated upon coordination to a Fe^{2+} centre.

Previously we have found that both intra- and extra-diol oxygenations are catalysed by a bipyridine(pyridine)iron complex.[4] We here report that the oxygenations to form **2**–**5** in eqn. (1) are catalysed by $FeCl_2$ or $FeCl_3$ in the presence of a small amount of water (without addition of further ligands) and that the extradiol oxygenation proceeds in preference to the intradiol oxygenation. Interestingly, the extradiol oxygenation is much more selective for Fe^{2+} than for Fe^{3+}. The different effect of the water concentration on the intra- and extra-diol oxygenations indicates that the intermediates for the two reactions are different.

Oxygenations were performed in a 20 cm^3 cylindrical flask at 25 °C and 1 atm O_2. In a typical case, the reaction was initiated by addition of H_2O (0.18 cm^3) and THF (9.82 cm^3) to $FeCl_2$ (25 mg, 0.20 mmol) or $FeCl_3$ (32 mg, 0.20 mmol) and **1** (133 mg, 0.60 mmol) in the flask. The solution was stirred magnetically and products extracted with CH_2Cl_2 were quantitatively analysed by ^1H NMR. This was performed by the gravimetric method, *i.e.*, weights of pieces of paper in the shapes of specific ^1H NMR peaks[4] of products cut from their expanded copies were compared with that of the methyl peak of toluene. The usual integration method on the NMR recorder is not useful because a mixture of products exhibited



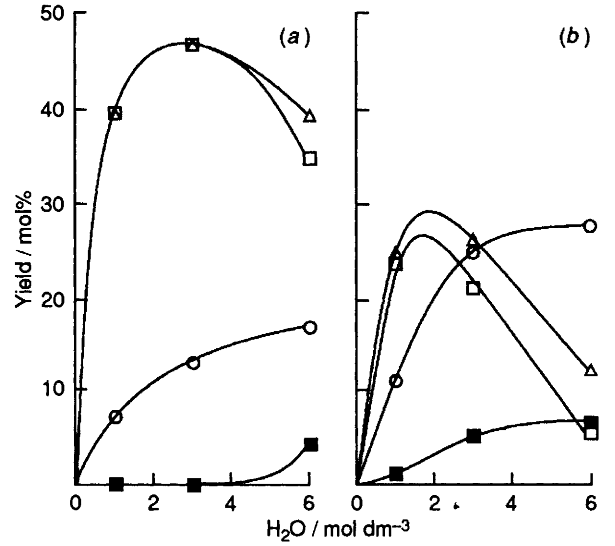


Fig. 1 Effect of the water concentration on the intra- and extra-diol oxygenations of **1** by $FeCl_2$ and $FeCl_3$ in THF–H_2O. (*a*) $FeCl_2$ or (*b*) $FeCl_3$ (0.20 mmol), **1** (0.60 mmol), THF + H_2O (10 cm^3), 1 atm O_2, 25 °C. Yields formed after 100 min, based on [Fe]. (○) Intradiol **2**, (□) extradiol **4**, (■) extradiol **5**, (△) **4** + **5**

Table 1 Oxygenation of DTBC catalysed by iron chlorides in THF–H_2O and THF–py[a]

			Yields of products/mol %[d]		
			Intra- and extra-diol	Others	
Iron chloride	Additive[b]	Conv.[c]	**2**–**5** (**2**:**3**:**4**:**5**)	**6**–**8** (**6**:**7**:**8**)	**9**
$FeCl_2$	H_2O	97	46.8 (16:0:84:0)	12.6 (14:66:0)	128
$FeCl_3$	H_2O	75	46.8 (31:0:66:3)	27.3 (9:87:4)	132
$FeCl_2$	py	92	42.1 (45:17:5:33[e])	24.5 (7:79:14)	155
$FeCl_3$	py	91	40.6 (35:39:0:26[e])	19.6 (0:90:10)	182

[a] $FeCl_2$ or $FeCl_3$ (0.20 mmol), **1** (0.60 mmol), THF + H_2O (or py) (10 cm^3), 1 atm O_2, 25 °C. [b] H_2O or py (10 mmol). [c] Conversion of **1**. [d] Yields formed after 100 min, based on [Fe]. [e] **5** was partly converted to 3,5-di-*tert*-butyl-5-formylfuran-2-one.

many peaks in the similar region. Reactions were also performed in the presence of pyridine in place of H_2O. Table 1 shows the results after 100 min. Identified products other than the intradiol oxygenation (**2** and **3**) or extradiol oxygenation products (**4** and **5**) were **6**–**9** in which quinone **9** was formed in the highest yield. Yields of the oxygenated products were slightly greater in THF–H_2O than in THF–py. In THF–H_2O, the extradiol oxygenation products (**4** + **5**) were much more abundant than the intradiol (**2**), especially in the case of $FeCl_2$. It is characteristic that the dioxygenated product, **3**, is not formed in THF–H_2O. In THF–py (**2** + **3**) was greater than (**4** + **5**) both with $FeCl_2$ and $FeCl_3$, but extradiol oxygenation (**4** + **5**) was promoted by $FeCl_2$ than $FeCl_3$.

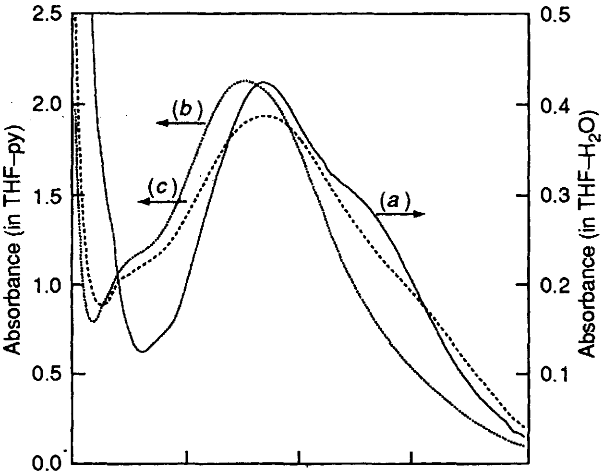
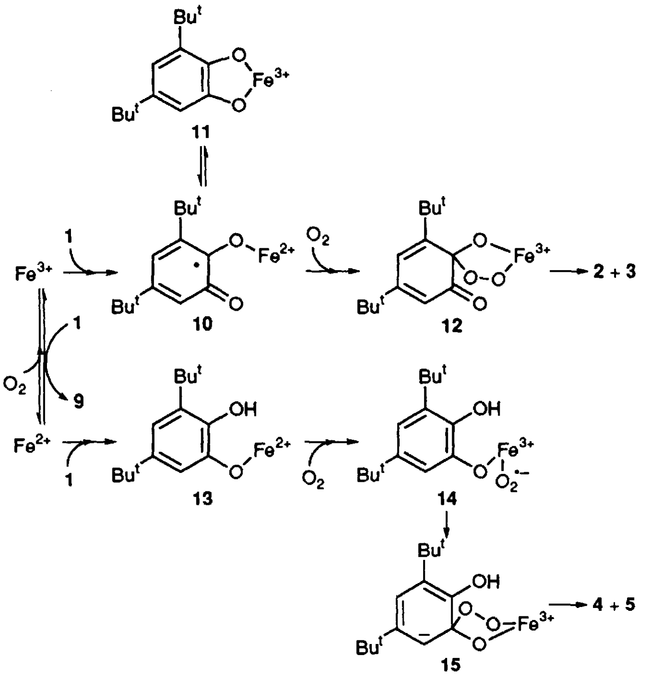


Fig. 2 Electronic spectra of complexes formed by the reaction of $FeCl_3$ with **1** in THF–H_2O and THF–py.$FeCl_3$ (0.20 mmol), **1** (0.60 mmol), THF + H_2O (or py) (10 cm^3), in Ar. (*a*) H_2O (20 mmol), (*b*) py (1 mmol), (*c*) py (10 mmol)



Scheme 1

Fig. 1 shows the effect of the concentration of water in THF–H_2O. The reaction did not proceed in the absence of water and was promoted by increasing concentration of water. Differently from the intradiol oxygenation, extradiol oxygenation was inhibited by high concentrations of water, remarkably so in the case of $FeCl_3$. Electronic spectra indicated the coordination of **1** to iron in argon (Fig. 2). For $FeCl_3$ the spectrum in THF–H_2O is similar to that in THF–py though the peak intensity of the former is much smaller. Since the spectra were not observed in the absence of water or pyridine it is clear that these solvents are required to deprotonate (and thus coordinate **1** to Fe^{3+}), as well as stabilizing the complex by ligation. In THF–py, increasing the concentration of pyridine causes a red shift of the peak, indicating the formation of an octahedral complex with more coordinated pyridine molecules.[5] The shoulder observed in THF–H_2O may correspond to a similar type of complex, but the intensity of the shoulder does not increase with increasing concentration of water. For $FeCl_2$, the same spectra were observed but only after introduction of oxygen. The solutions exhibiting the spectra as shown in Fig. 2 also show in their ESR spectra a characteristic single line peak at g = 2.01 corresponding to a 3,5-di-*tert*-butylbenzosemiquinonate–Fe^{2+} species (**10**), which is coordinated by chloride ligands and has a vacant site for coordination (five-fold coordination, probably pentagonal bipyramidal).[5,6] At high concentrations of pyridine, formation of an octahedral catecholatoiron complex is shown by peaks at g = 4.20 and 8.99.

Scheme 1 rationalises the intra- and extra-diol oxygenations catalysed by Fe^{3+} and Fe^{2+} species, respectively, similarly to the enzymatic systems. For $FeCl_3$, an iron(II) species is formed in the oxidation of **1** to quinone **9**. On the other hand, for $FeCl_2$, an iron(III) species is formed by oxidation of Fe^{2+} with O_2. Reaction of **1** with Fe^{3+} leads to a fairly stable complex, **10**, which is in equilibrium with **11**. **10** gives only the intradiol oxygenation products by insertion of O_2, probably *via* **12**. For the extradiol oxygenation, there is no direct evidence for coordination of **1** to Fe^{2+}, but it may occur prior to that of O_2.[7] As suggested by a molecular orbital calculation study,[8] the coordinated oxygen ($-O_2^{-\cdot}$) in **14** binds to C(1) to form **15**, while the free oxygen may attack C(2) probably to form **13**. The enhanced stability of **10** contributes to promote the intradiol oxygenation even in the $FeCl_2$ system as seen in THF–py; on the contrary, the extradiol oxygenation is promoted when **10** is unstable as seen in THF–H_2O.

We thank the Ministry of Education, Science, and Culture for Grants.

Received, 22nd March 1994; Com. 4/01719F

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